IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: James Ronald Lawter and Stephen J. Comiskey

Serial No.: Continuation of 09/661,836

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For: FORMULATIONS FOR TREATING OR PREVENTING MUCOSITIS

Box Patent Application
U.S. Patent and Trademark Office
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PRELIMINARY AMENDMENT

Sir:

Prior to examination, please amend the application as follows.

In the Specification

On page 1, after the title and before "Field of the Invention", please insert the following heading and paragraph.

--Cross-Reference to Related Applications

This application is a continuation of pending prior application U.S. Serial No. 09/661,836 filed September 14, 2000, which claims priority to U.S. Serial No. 60/153,892 filed September 14, 1999.--

On page 1, please delete lines 6-7.

In the Claims

1. (amended) A pharmaceutical composition [for treating or preventing mucositis] comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

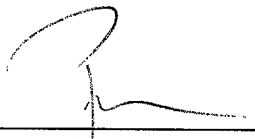
24. (amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising making a formulation for topical administration [to the mucosa] of an effective amount of a tetracyline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally administered.

Remarks

Applicants have attached a marked-up version of page 1 of the Specification, and a clean copy of page 1 of the Specification with the changes incorporated.

The claims have been amended to incorporate the limitations of claim 9 into the independent claims.

Respectfully submitted,



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Date: December 4, 2001

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this paper and any documents referred to as attached or enclosed are being deposited with the United States Postal Service on this date, December 4, 2001, in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10, Express Mail Label No. EL 639 985 041 US, addressed to Box Patent Application, U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202.

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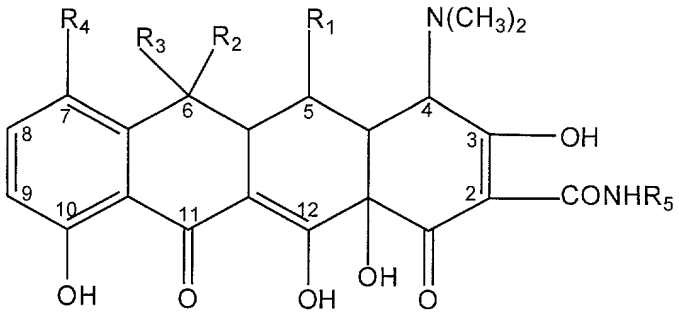
Date: December 4, 2001

Marked-Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (amended) A pharmaceutical composition [for treating or preventing mucositis] comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration [to the mucosa] wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

2. The composition of claim 1 wherein the tetracycline is selected based on poor oral absorption from the group consisting of tetracyclines defined by the following structure:



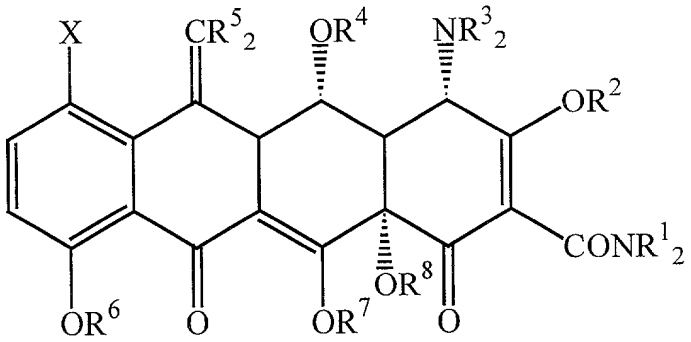
wherein R_1-R_5 may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

3. The composition of claim 2 wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a halogen, or a nitrogen containing entity; and R_5 is a hydrogen atom, or nitrogen containing ring structure.

4. The composition of claim 2 wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

5. The composition of claim 2 wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12.

6. The composition of claim 2 having the following structure:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6 wherein R^1, R^2, R^4, R^5, R^6, R^7, and R^8 are H; wherein R^3 is CH_3; and wherein X is a chloro group.

8. The composition of claim 1 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

9. The composition of claim 1 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions.

10. The composition of claim 9 wherein the tetracycline is formulated as a dry powder.

11. The composition of claim 1 wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered to the mouth and then swallowed.

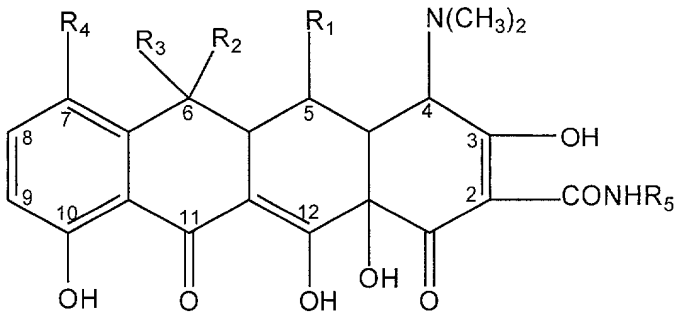
12. The composition of claim 8 wherein the tetracycline is in the form of a polyvalent metal ion complex.

13. The composition of claim 12 wherein the polyvalent metal ion is calcium or magnesium.

14. The composition of claim 1 wherein the tetracycline is formulated to be topically administered to the mucosa as an aerosol.

15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline <u>in the form of a polyvalent metal ion complex</u> in a carrier for topical administration [to the mucosa] <u>wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered</u>.

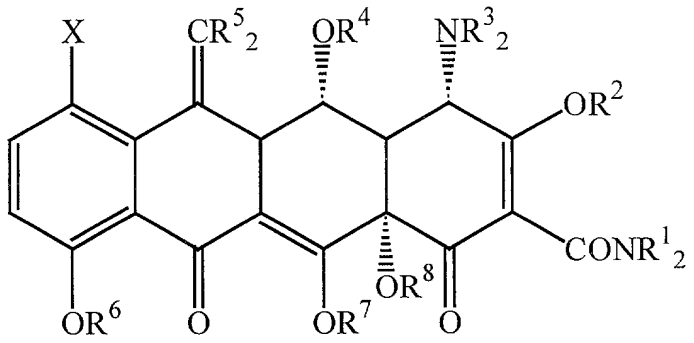
16. The method of claim 15 wherein the tetracycline is selected based on poor absorption from the group consisting of tetracyclines defined by the following structure:



wherein R_1-R_5 may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

17. The method of claim 15 wherein the tetracycline is selected from the group consisting of compounds with the formula wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a halogen, or a nitrogen containing entity and R_5 is a hydrogen atom, or nitrogen containing ring structure, compounds wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12, and compounds wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

18. The method of claim 16 wherein the tetracycline has the following structure:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

19. The method of claim 18 wherein the tetracycline is meclocycline, wherein R^1, R^2, R^4, R^5, R^6, R^7, and R^8 are H;

wherein R^3 is CH_3; and wherein X is a chloro group.

20. The method of claim 15 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

21. The method of claim 15 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions, comprising suspending or dissolving the tetracycline and carrier in a liquid for adminstration of the tetracycline to the patient.

22. The method of claim 15 wherein the tetracycline is administered daily starting at least one day before the patient is treated with radiation or chemotherapy.

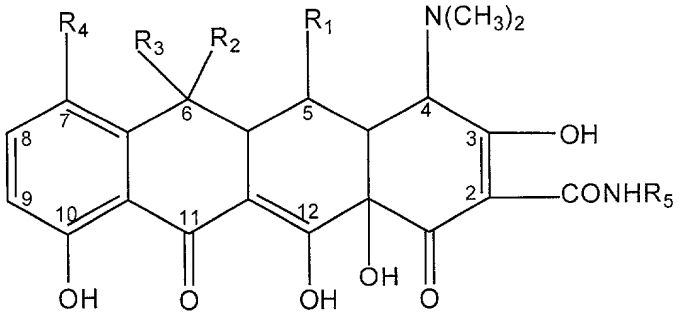
23. The method of claim 15 wherein the patient is treated between one and six times daily.

24. (amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising making a formulation for topical administration [to the mucosa] of an effective amount of a tetracyline <u>in the form of a polyvalent metal ion complex</u> which has less than 10% bioavailability when orally administered.

Clean Copy of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(i)

1. (amended) A pharmaceutical composition comprising an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

2. The composition of claim 1 wherein the tetracycline is selected based on poor oral absorption from the group consisting of tetracyclines defined by the following structure:



wherein R_1-R_5 may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

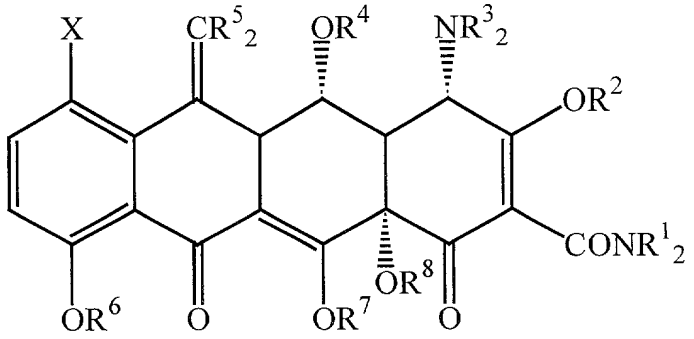
3. The composition of claim 2 wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a

halogen, or a nitrogen containing entity; and R_5 is a hydrogen atom, or nitrogen containing ring structure.

4. The composition of claim 2 wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

5. The composition of claim 2 wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12.

6. The composition of claim 2 having the following structure:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

wherein X is an H, alkyl, alkoxy, phenoxy, aryloxy, amino group, amide, acyl, and halo group; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6 wherein R^1, R^2, R^4, R^5, R^6, R^7, and R^8 are H;

wherein R^3 is CH_3; and wherein X is a chloro group.

8. The composition of claim 1 wherein the carrier for topical administration to the mucosa of the oral cavity and gastro-intestinal tract is selected from the group consisting of a mouthwash, lozenge, tablet, paste and gel.

9. The composition of claim 1 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions.

10. The composition of claim 9 wherein the tetracycline is formulated as a dry powder.

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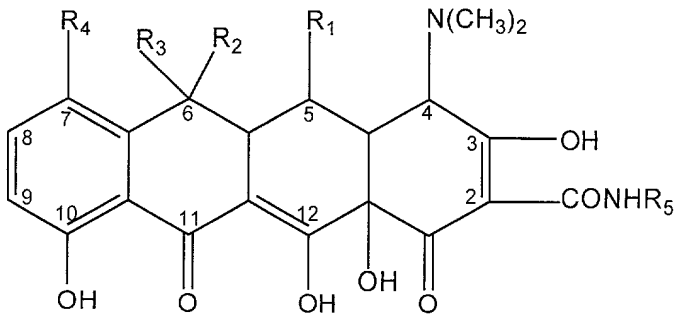
12. The composition of claim 8 wherein the tetracycline is in the form of a polyvalent metal ion complex.

13. The composition of claim 12 wherein the polyvalent metal ion is calcium or magnesium.

14. The composition of claim 1 wherein the tetracycline is formulated to be topically administered to the mucosa as an aerosol.

15. (amended) A method for treating a patient in need thereof comprising administering to the patient an effective amount of a poorly absorbed tetracycline in the form of a polyvalent metal ion complex in a carrier for topical administration wherein less than 10% of the tetracycline is absorbed into the systemic circulation when topically administered.

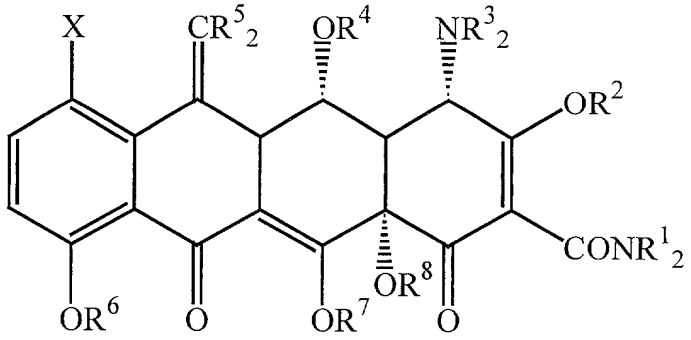
16. The method of claim 15 wherein the tetracycline is selected based on poor absorption from the group consisting of tetracyclines defined by the following structure:



wherein R_1-R_5 may be a hydrogen atom, a halogen atom, a hydroxyl group, or any other organic composition comprising from 1-8 carbon atoms and optionally include a heteroatom such as nitrogen, oxygen, in linear, branched, or cyclic structural formats.

17. The method of claim 15 wherein the tetracycline is selected from the group consisting of compounds with the formula wherein R_1 and R_2 are hydrogen or a hydroxyl group; R_3 is hydrogen or a methyl group; R_4 is a hydrogen atom, a halogen, or a nitrogen containing entity and R_5 is a hydrogen atom, or nitrogen containing ring structure, compounds wherein the tetracycline is modified at any of positions 1 through 4 and 10 through 12, and compounds wherein the tetracycline is modified by substitution of H at carbon 9 by a substituted amido group.

18. The method of claim 16 wherein the tetracycline has the following structure:



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 can be H, C1-C3 alkyl, phenyl, and aryl groups; and

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21. The method of claim 15 wherein the carrier for topical administration comprises the tetracycline coated onto or encapsulated into a carrier selected from the group consisting of powders, pellets, microcapsules, liposomes, and emulsions, comprising suspending or dissolving the tetracycline and carrier in a liquid for adminstration of the tetracycline to the patient.

22. The method of claim 15 wherein the tetracycline is administered daily starting at least one day before the patient is treated with radiation or chemotherapy.

23. The method of claim 15 wherein the patient is treated between one and six times daily.

24. (amended) A method for making a composition for treating a patient to prevent or treat mucositis comprising making a formulation for topical administration of an effective amount of a tetracyline in the form of a polyvalent metal ion complex which has less than 10% bioavailability when orally administered.

Marked-up Copy of Amended Specification Page 1
Pursuant to 37 C.F.R. § 1.121(b)(1)(iii)

FORMULATIONS FOR TREATING OR PREVENTING MUCOSITIS

Cross-Reference to Related Applications

This application is a continuation of pending prior application U.S. Serial No. 09/661,836 filed September 14, 2000, which claims priority to U.S. Serial No. 60/153,892 filed September 14, 1999.

Field of the Invention

The present application relates generally to formulations containing a tetracycline that are useful for treating or preventing mucositis.

[This application claims priority to U.S.S.N. 60/153,892 filed September 14, 1999.]

Background of the Invention

Mucositis is a dose-limiting side effect of cancer therapy and bone marrow transplantation and is not adequately managed by current treatment (Sonis, 1993a, "Oral Complications," in: *Cancer Medicine,* pp. 2381-2388, Holand et al.; Eds., Lea and Febiger, Philadelphia; Sonis, 1993b, "Oral Complications in Cancer Therapy," In: *Principles and Practice of Oncology*, pp. 2385-2394, De Vitta et al., Eds., J. B. Lippincott, Philadelphia). Oral mucositis is found in almost 100% of patients receiving radiotherapy for head and neck tumors, in about 40% of patients receiving chemotherapy, and in about 90% of children with leukemia (Sonis, 1993b, supra). Complications related to oral mucositis, though varying in the different patient populations, generally include pain, poor oral intake with consequent dehydration and weight loss, and systemic infection with organisms originating in the oral cavity leading to septicemia (Sonis, 1993b; U.S. patent No. 6,025,326 to Steinberg et al.). In addition to the oral cavity, mucositis may also affect other parts of the gastro-intestinal tract.

A variety of approaches to the treatment of oral mucositis and associated oral infections have been tested with limited success. For example, the use of an

Clean Copy of Amended Specification Page 1
Pursuant to 37 C.F.R. § 1.121(b)(1)(ii)

FORMULATIONS FOR TREATING OR PREVENTING MUCOSITIS

Cross-Reference to Related Applications

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A variety of approaches to the treatment of oral mucositis and associated oral infections have been tested with limited success. For example, the use of an allopurinol mouthwash, an oral sucralfate slurry, and pentoxifyline were reported in preliminary studies to result in a decrease in mucositis. Subsequent